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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,130	03/07/2000	Robert Arathoon	P1099R2	1353

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EXAMINER
HOLLERAN, ANNE L

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/19/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/520,130	ARATHOON ET AL.
	Examiner	Art Unit
	Anne Holleran	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,16-18,31 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,16-18,31 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

14)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)

3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

DETAILED ACTION

1. The amendment filed August 9, 2002 is acknowledged. Claims 12-14, 16-18, 31 and 33-38 were amended.

Claims 12-14, 16-18, 31 and 33-38 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

3. The rejection of claims 16 and 17 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

Claim Rejections Maintained and New Grounds of Rejection:

4. The rejection of claims 12-14, 16-18, 31, and 33-38 under 35 U.S.C. 112, first paragraph, on the grounds that the specification is not enabling for the full scope of the claimed inventions is maintained.

Applicant's arguments are unpersuasive. The amendments to the claims are insufficient to overcome the rejection.

[illegible] each of the two polypeptides may be identical because the claims recite that either the first or the

second polypeptide comprises either a first or second light chain. The first and second light chains must be at least 80 percent identical to each other. Because of the way the claims are drawn, the first and second polypeptides may both comprise the first light chain, or both comprise the second light chain, or one polypeptide may comprise the first light chain and the other may comprise the second light chain.

The specification confines its examples to how to screen scFv libraries to find antibody pairs that could be used in bispecific scFv constructs where the light chain is identical. The specification fails to teach how to make such bispecific antibodies, and only teaches how to screen an scFv library for the purpose of discovering heavy and light chain pairings, where one light chain binds to two different heavy chains to make a binding domain that binds to different antigens. The specification fails to teach examples where, after finding such a heavy and light chain pairings, the light chain sequence is then altered and then the altered light chain retains the ability to pair with either heavy chain and the resulting binding domains bind antigen.

As set forth in the previous office action, minor modifications in the binding domain of an antibody may lead to drastic changes in antigen binding ability. Thus, the art of antibody engineering appears to be highly unpredictable and one of skill in the art would not have a reasonable expectation for success in how to make the full scope of the claimed antibodies.

It is noted also that with regard to how to use the claimed invention, the specification confines its discussion to general terms. The specific example of a bispecific antibody with

5. The rejection of claims 12-14, 16-18, 31 and 33-38 under 35 U.S.C. 112, first paragraph, on the grounds that the applicant was not in possession of the claimed inventions at the time of filing, because the disclosure of the specification fails to adequately describe the claimed genus of compounds is maintained.

Applicant's arguments are unpersuasive. The amendments to the claims are insufficient to overcome the rejection.

The claims are drawn to bispecific antibodies that bind to any two different antigens, and comprise two polypeptides that each comprise a heavy and light chain and a multimerization domain. The two possible light chains that may be used to make either of the polypeptides must be at least 80 percent identical in amino acid sequence.

Applicant argues that the specification presents more than one example of possible scFv pairs having different antigen binding specificity but sharing a light chain. However, these examples are not representative of the claimed genus because the claimed genus of bispecific antibodies comprise scFv pairs that bind any antigen and because the claimed genus of bispecific antibodies comprise scFv pairs where the light chains are not identical but are closely related in structure. While the specification generally contemplates such scFv pairs, the specification does not describe such pairs structurally nor gives specific directions for how to make such antibodies.

6. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

Claim 14 is indefinite because the phrase "the original nucleic acid" lacks antecedent basis in claim 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 12-14, 16-18, 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaughan (Nature Biotechnology, 14: 309-314, 1996; cited in the IDS) in view of Bosslet (U.S. Patent 5,591,828; issued Jan. 7, 1997; effective filing date of 6/20/1990) and further in view of either Ridgway (Protein Engineering, 9: 617-621, 1996), Carter (U.S. Patent 5,807,706; issued September 15, 1998; effective filing date of March 1, 1995) or Carter (WO 96/27011; published September 1996; cited in the IDS).

Vaughan teaches an example of two scFvs where identical light chains are paired with two different heavy chains to bind to two different antigens, DTPA and CEA.

Vaughan fails to teach a bispecific antibody made from the two scFvs.

Bosslet teaches bispecific antibodies where one specificity is to an anti tumor antigen and the other is to a chelating agent such as DTPA (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody using the scFvs for DTPA and CEA as taught by Vaughan. One would have been motivated to have make such a bispecific scFv because CEA is a known cancer antigen and DTPA is a known chelating agent often used to chelate radioactive moieties. Thus, the bispecific pairing of anti-CEA with anti-DTPA would be used to target tumors bearing the CEA antigen with radioactive moieties chelated via the DTPA binding portion of the bispecific scFv.

Neither Vaughan nor Bosslet teaches bispecific antibodies that comprise multimerization

[illegible] protein engineering

multimerization domains comprising antibody CH3 regions onto polypeptides comprising heavy

and light chain variable domains of antibodies and teach making bispecific antibodies (see abstract, page 620, col. 2, fourth full paragraph of Ridgway; abstract of Carter (U.S.); page 6-7 of Carter (WO)). The Knobs and Holes multimerization domain of Ridgway , Carter (U.S.) or Carter (WO) forms an interface in which the interaction is between a cavity of one multimerization domain and a protuberance of a second multimerization domain. Carter (WO) teaches a composition comprising a heteromultimer and a pharmaceuticaly acceptable carrier (claim 28, page 58).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have engineered a bispecific antibody by the method of Ridgway, Carter (U.S.) or Carter (W.O). One would have been motivated to use the methods of Ridgeway, Carter (U.S.) or Carter (WO) because of the benefits of using such domains when making bispecific antibodies.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Patent Examiner
November 18, 2002